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Detecting and monitoring cellular and molecular changes associated with cancer are essential to the verification of cancer treatment. In this investigation we show that modulated electron radiation therapy can in principle conform a region of high dose to a volume of malignant breast tissue. Currently available means to both measure the malignant volume and record progression of its response to radiation are limited. We therefore chose to explore another means to determine the breast treatment target; optical tomography. Using the fact that mammalian tissues transmit light at a low level and emit virtually no light at all, optical signatures conferred on tumor cells by expression of reporter genes can be detected externally by photon-detecting systems.
In this paper we study a first approach to a gradient-based iterative procedure using a finite-difference scheme as forward model. We provide results at the current state of research and discuss ways to address current limitations.

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Introduction

Detecting and monitoring cellular and molecular changes associated with cancer are essential to our understanding of neoplasia and to the verification of its treatment. In this investigation we show that modulated electron radiation therapy can in principle conform a region of high dose to a volume of malignant breast tissue. Currently available means to both measure the malignant volume and record progression of its response to radiation are limited. We therefore chose to explore another means to determine the breast treatment target; optical tomography. Using the fact that mammalian tissues transmit light at a low level and emit virtually no light at all, optical signatures conferred on tumor cells by expression of reporter genes can be detected externally by photon-detecting systems.

The realization of such in vivo optical imaging therefore requires three components: (1) a fast and accurate measurement means of near-infrared (NIR) light; (2) a computationally-efficient reconstruction algorithm and (3) the existence of a significant contrast in the optical properties of the medium that we are reconstructing. For (3), expression of reporter genes such as the bioluminescent enzyme firefly luciferase can effectively modify tumor cells optical properties, thus securing sufficient contrast between the tumor and the rest of the medium.

As far as the inversion algorithm (2) is concerned, most current efforts have been hampered by the computationally-intensive nature of a full three-dimensional data inversion.
In order to achieve a first simple and robust method, a gradient-based reconstruction algorithm was investigated to invert a bioluminescence problem and compute the shape of a bioluminescent tumor. A similar approach is described in article [1].

This method was implemented through an iterative procedure that falls into four distinctive steps: we successively (1) chose an initial source distribution; (2) computed its response a forward model; (3) computed an objective function (which estimates the distance between our 'guessed' source distribution and the actual one) and computed the gradient of the objective function with respect to the source intensity distribution and (4) moved along the gradient direction until we found a closer distribution and updated the source distribution. The iterative feature naturally came from the fact that steps (2)-(4) was performed repeatedly until our computed source distribution produced a signal that was 'close enough' (we will discuss later what that means) to the actual measurement. This procedure was implemented on Matlab and is represented in figure 1.

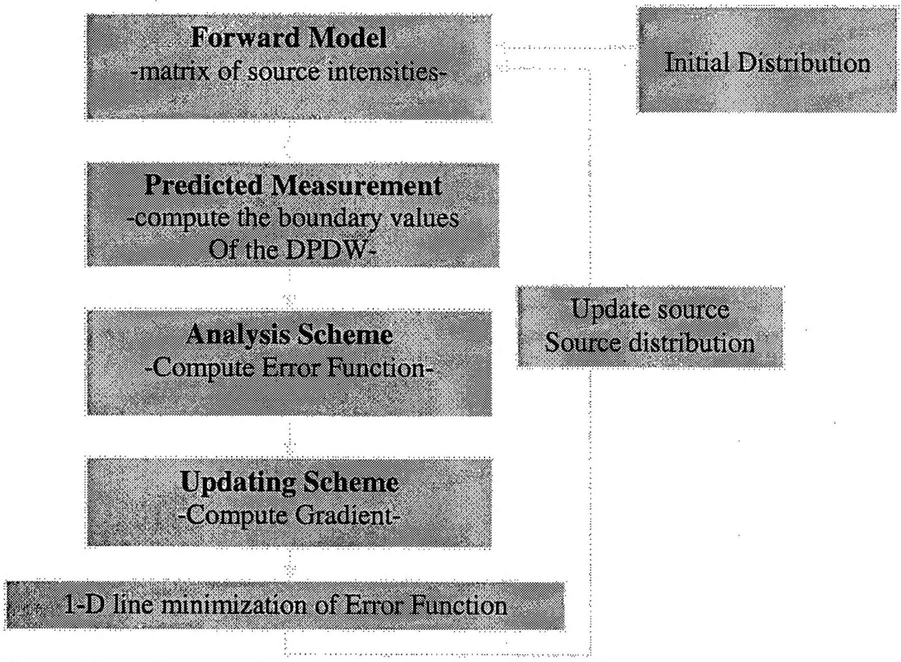

fig 1: flow diagram of the gradient-based iterative procedure

In highly scattering media such as biological tissue, light propagation is well approximated by the photon diffusion equation, which is as follows:

$$\nabla^2 U(r,t) - \frac{\upsilon\mu_a}{D} U(r,t) - \frac{1}{D}\frac{\partial U(r,t)}{\partial t} = -\frac{\upsilon}{D} S(r,t), \quad (1)$$

Where $U(r,t)$ is the photon fluence rate [photons/cm^{2}s], μ_a and μ_s are the absorption and scattering coefficients, respectively. $D = \upsilon / 3\mu_s$ is the photon diffusion coefficient, and $S(r,t)$ is the number of photon emitted by the source (tumor) at position *r* and time *t*.
Equation (1) is actually a particular case of a more general one:

$$\frac{\partial U}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial U}{\partial x}\right) + \frac{\partial}{\partial y}\left(D\frac{\partial U}{\partial y}\right) - c\mu_a U + S, \qquad (2)$$

in which we now assume that the diffusion coefficient *D* is constant and uniform.
At this point, we need to use a forward model to compute the system's response to a given source distribution.

I - The forward model and Predicted Measurement:

1. Using the method described in article [2], the propagation of light intensity is assumed to be a simple spherical damped wave, i.e. described by:

$$\phi_0(r,r_s) = \frac{\upsilon M_0}{D}\frac{\exp(ik|r-r_s|)}{4\pi|r-r_s|}$$

With such assumption, we can compute the system's response to any distribution of source by just considering the distribution as the sum of local source and using the

superposition principle. Indeed, since equation (1) is linear in the source and $\phi(r,t)$, the response to a sum of point sources is simply the sum of the responses to each point source.

2. The second approach is much more realistic and uses a finite-difference scheme to compute the response. Thus equation (1) is solved by replacing the temporal and spatial derivatives by their finite-difference approximations:

$$\frac{\partial U}{\partial t} \approx \frac{U^n - U^{n-1}}{\Delta t}$$

We similarly have that:

$$\frac{\partial}{\partial x}\left(D\frac{\partial U}{\partial x}\right) \approx D\frac{U_{i+1,j} - U_{i-1,j}}{\Delta x^2}, \quad \frac{\partial}{\partial y}\left(D\frac{\partial U}{\partial y}\right) \approx D\frac{U_{i,j+1} - U_{i,j-1}}{\Delta y^2}$$

As explained in article [1], different possibilities arise when it comes to discretizing a continuous differential equation. In particular, two finite-difference schemes are particularly natural: the explicit scheme, which expresses the current state (n+1) in terms of the previous state (n), and the implicit scheme, which expresses the future state in terms of the current one. The explicit scheme is the simplest since it computes the current state only from parameters that we already know (i.e. the past state), but further study proves that it is only conditionally-stable. On the other hand, the implicit scheme involves more computation but turns out to be unconditionally-stable. I followed the method chosen in Article [1], which tries to get the best of both worlds by using an Alternation-Direction Implicit (ADI) scheme. In the ADI method, the computation of U^{n+1} from U^n is split in two steps. In the first half-time step, the spatial derivative in only one (say x) direction is evaluated at the present time step (implicit) and the other spatial derivative (say y) is evaluated in the previous time-step (explicit). In the next half-time step, the implicit and explicit directions are switched.

According to this scheme, equation (1) is discretized and it can then be shown that equation the relationship between U^n and $U^{n+1/2}$ can be expressed in the following matrix form:

$$\begin{aligned} AU^{n+1/2} &= BU^n + S^{n+1/2} \\ U^{n+1/2} &= A^{-1}BU^n + A^{-1}S^{n+1/2} \end{aligned} \qquad (3)$$

where $U^{n+1/2}$ is an intermediary state. A similar relationship is then found between $U^{n+1/2}$ and U^{n+1}.

II - Analysis Scheme:

The analysis scheme only consists in the calculation of the objective function ϕ, which is simply the sum of the squared differences between the computed signal and the actual, measured one. This is naturally a function of the distribution of sources, denoted ζ.

$$\phi(\zeta) = \sum_{s \in M} \left(Y_s^n - U_s^n(\zeta)\right)^2 \qquad (4)$$

III - Updating Scheme:

This is where we turn to the computation of the gradient. This part is naturally the most computationally-heavy. The derivative of the objective function with respect to the source distribution ζ is given by:

$$\frac{\partial \phi}{\partial \zeta_r} = \sum_{n \in T} \sum_{p \in \Omega} \frac{\partial \phi}{\partial U_n^p} \frac{\partial U_n^p}{\partial \zeta_r}$$

where n represents the time steps and p is the index of a grid point. If we consider a single time step, this simplifies to:

$$\frac{\partial \phi}{\partial \zeta_r} = \sum_{p \in \Omega} \frac{\partial \phi}{\partial U_n^p} \frac{\partial U_n^p}{\partial \zeta_r}, \qquad (5)$$

The first part, which is the derivative of the error function with respect to the intensity, comes easily if we remember that the error function only depends on the intensity at grid point p if p is on the boundary, ie if it is part of the measurement set. In this particular case, the error function is a simple quadratic function of the intensity, and we thus have:

$$\frac{d\phi}{dU^p} = \frac{\partial \phi}{\partial U^p} = \begin{cases} -2\left(Y_p - U^p\right) & , p \in M \\ 0 & otherwise \end{cases} \qquad (6)$$

Now, the signal's derivative with respect to the source distribution naturally depends on the assumption made for the forward model.

1. In the framework of article [2], this derivative follows directly from our assumption:
$$\frac{\partial \phi}{\partial \zeta_r} = \sum_{p \in M} -2\left(Y_p - U^p\right) \frac{\upsilon}{D} \frac{\exp\left(ik\left|r_p - r_r\right|\right)}{4\pi\left|r_p - r_r\right|} \quad (11)$$
2. In the finite-difference forward model, this gradient computation is naturally more involved and requires additional care. In particular, one interesting way is to use equation (3) to see that, if we consider (3) a time *n-1/2* and *n* instead of *n* and *n+1/2*, we get:
$$\frac{\partial A}{\partial \zeta_r} + A \frac{\partial U^n}{\partial \zeta_r} = \frac{\partial B}{\partial \zeta_r} U^{n-1/2}$$
$$\text{thus } \frac{\partial U^n}{\partial \zeta_r} = A^{-1}\left(\frac{\partial B}{\partial \zeta_r} U^{n-1/2} - \frac{\partial A}{\partial \zeta_r} U^n \right) \quad (7)$$
which can be easily calculated by since we know the intensity U and the matrices A and B. This method is yet to be implemented this method but it promises to be more adapted to our problem than 1, which is over-simplifying.

IV – Line minimization:

Once we have the vector $\left(\partial \phi / \partial \zeta_r\right)_{r \in M}$ for a current position ζ_0, we can move along the direction defined by $\left(\partial \phi / \partial \zeta_r\right)_{r \in M}$ and look for the position that yields the smallest objective function possible. This line minimization that we used does not systematically yield the global minimum

in theory. However, it turned out to be very fast and accurate and worked in all of the practical range of physically-relevant cases (besides, it can easily be modified to be made systematic). It consists in choosing an initial step size $\Delta\zeta$ and computing the error function along consecutive values within the segment $[\zeta_0 - \partial\phi/\partial\zeta_r ; \zeta_0 + \partial\phi/\partial\zeta_r]$, until we find three consecutive values that $\zeta_{v-1}, \zeta_v, \zeta_{v+1}$ such that $\Phi(\zeta_{v-1}) > \Phi(\zeta_v)$ and $\Phi(\zeta_v) < \Phi(\zeta_{v+1})$. We then reduce the step size and continue until the segment bracketing the minimum is as narrow as desired.
Gradient computation and line minimization are then performed repeatedly until the gradient becomes null (and we have reached the optimal source distribution) or, most likely, until the last iterations results in an insignificant change of the objective function (i.e. below a given threshold)

Key Research Accomplishment :

For a total target size of 50*50, which is already quite simplistic, the typical computation time for about 10 iterations was initially of 6 hours (on Matlab, with a 400MHz PC) and then optimized down to 2 hours, which is still cumbersome.
We started with a single light-emitting source located in a 2D array at (0,0) (i.e. in the center of 50*50 matrix). The reconstruction scheme was initialized from a distribution of 9 sources located in the square [-1;1]*[-1;1]. For each step, we assumed that we could only access the intensity of light emitted at the boundary of the matrix, just like a photon-counting device would only be able to count the photons at the boundary of the medium

The source distribution obtained after 100 iterations by the method is shown in figure 2.

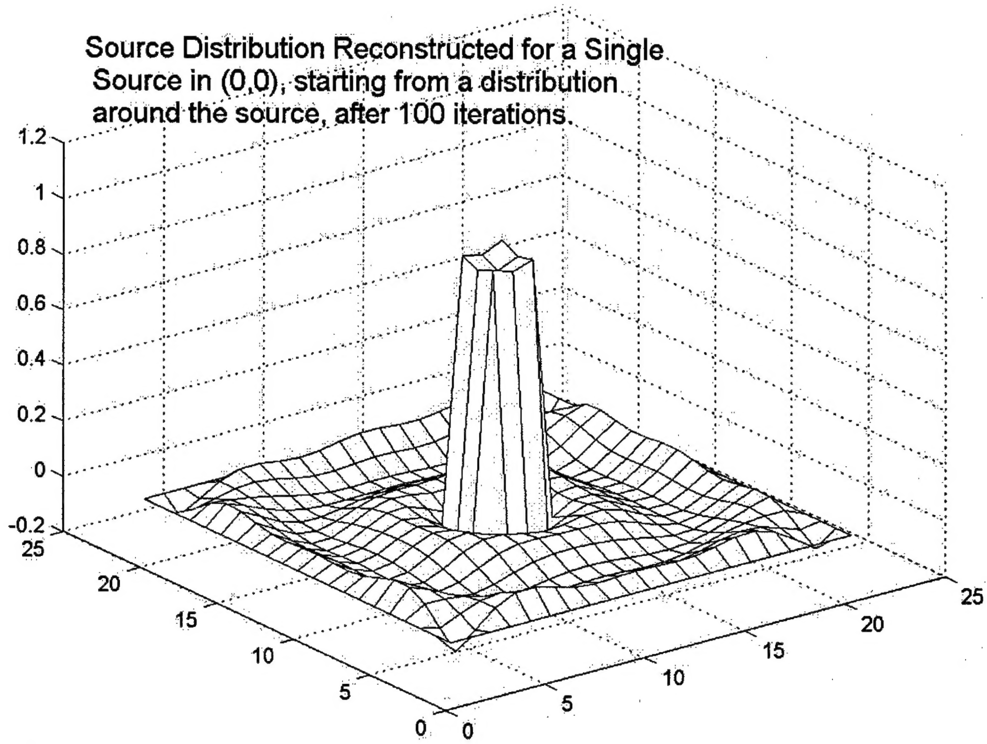

fig 2. : This is the source distribution that was reconstructed for a single source located at the center of the matrix (the x and y axes only reflect the indices of the matrix elements, not their 'actual' location), departing from an initial source distribution that was located in the 3*3 voxels around the center of the matrix.

Conclusion:

The basic iteration scheme can be applied to this problem. Further work is needed to improve the forward calculation to make it more physically realistic, and, in particular, the finite-difference scheme needs to be incorporated in the gradient computation. Future work should include the investigation of algorithm when the optical attenuation μ_a, optical scatter μ_s are spatially dependent.

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